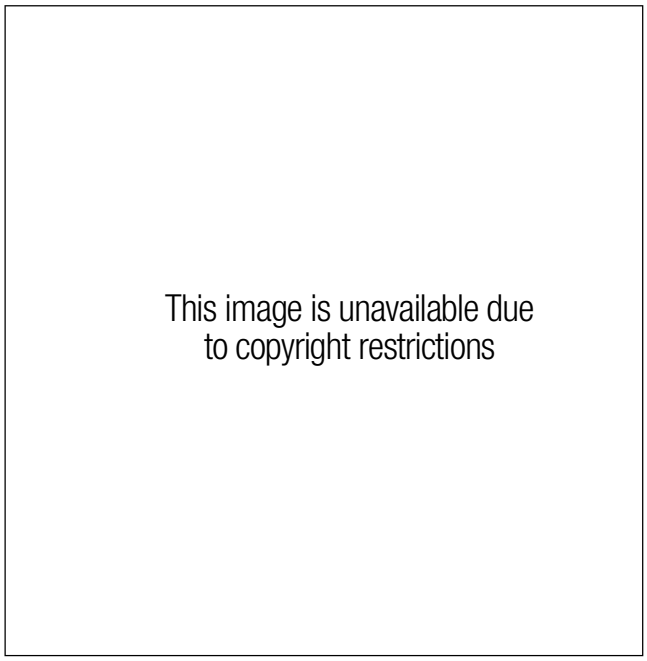
Rivastigmine transdermal patch for mild to moderately severe Alzheimer's disease

GIDEON CAPLAN MB BS, FRACP **LISA KELLY** MB BCh, MSc, MRCP

Rivastigmine transdermal formulation (Exelon Patch) demonstrates a significantly lower incidence of gastrointestinal side effects in trials to date and may help with compliance to medication in certain groups of patients with Alzheimer's disease.



Alzheimer's disease accounts for approximately 70% of dementias worldwide. In Australia, the percentage of the population with dementia increased to 1% in 2005. Unfortunately there is currently no cure for dementia, but pharmacological treatment for Alzheimer's disease has been available for over 10 years. Although the effect of treatment is only mild on average, some patients respond more clearly than others. Treatment can make a significant difference for many people with dementia as well as their carers.

Initial drug therapy in patients with mild, moderate and severe Alzheimer's dementia is with an acetylcholinesterase inhibitor (ACHEI). The aim of treatment is to improve cognitive function and behavioural and psychological symptoms of dementia, as well as manage activities of daily living. In patients with moderate to severe dementia, memantine (Ebixa) may also be added to the treatment regimen or used as a single agent. Memantine has recently received a PBS listing (authority required) for moderately severe Alzheimer's disease. (Patients should have a Mini-Mental State Examination [MMSE] of 10 to 14 and confirmation of the diagnosis must be made by a specialist physician or a psychiatrist prior to commencement of treatment.)

Rivastigmine (Exelon) was originally introduced in tablet formulation with the theoretical advantage of inhibiting both enzymes involved in the breakdown of acetylcholine (acetylcholinesterase and butyrylcholinesterase). However, there is little evidence of head-to-head trials comparing rivastigmine with other ACHEIs to demonstrate a clinical advantage. Essentially, there is so far no compelling evidence that any one ACHEI is better than another in the treatment of dementia. In practice, patients taking oral rivastigmine experienced worse gastrointestinal tolerability than with other ACHEIs and many patients were unable to tolerate a therapeutic dose of oral rivastigmine for a sustained period. The twice-daily formulation of oral rivastigmine can cause difficulty with compliance to the medication.

Rivastigmine transdermal formulation (Exelon Patch) demonstrates a significantly lower incidence of gastrointestinal side effects in trials to date and may help with compliance to medication in certain groups of patients with Alzheimer's disease.

What is rivastigmine transdermal patch?

Rivastigmine patch is the first transdermal treatment for dementia. It delivers the active compound directly to the systemic circulation, bypassing the gastrointestinal tract and smoothing out fluctuations in plasma drug concentrations. This reduces gastrointestinal side effects by approximately two-thirds. In drug trials, carers also reported a preference for applying patches over administering capsules to patients.

Associate Professor Caplan is an Associate Professor of Geriatric Medicine and Director of Post Acute Care Services and Geriatric Medicine at the Prince of Wales Hospital. Dr Kelly is a Clinical Fellow of Geriatric Medicine, Department of Geriatric Medicine at the Prince of Wales Hospital, Sydney, NSW.

continued

How is it used?

Rivastigmine transdermal patch is applied once daily to clean, dry, hairless skin on the trunk or upper limbs. Ideally, it can suit patients who are reluctant to take tablets. There are two sizes of the patch: a 5 cm^2 patch containing 9 mg rivastigmine that delivers 4.6 mg/24 hours; and a 10 cm^2 patch containing 18 mg rivastigmine that delivers 9.5 mg/24 hours. Treatment is initiated with the 5 cm^2 patch and if this is well tolerated then the dose can be increased to the 10 cm^2 patch after at least four weeks. The 10 cm^2 patch can be continued for as long as a therapeutic benefit for the patient exists.

Once applied, the patch will tolerate bathing and sweating associated with hot weather. It should be applied to a different area of the body each day to prevent local irritation and the previous day's patch should be removed before a new patch is applied.

Who is it suitable for?

Rivastigmine transdermal patch is listed on the PBS (authority required), as the sole PBS-subsidised therapy, for mild to moderately severe Alzheimer's disease. A specialist physician or psychiatrist must confirm the diagnosis. Patients must have an MMSE of 10 to 24. If the score is between 25 and 30, an Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog; which is a more comprehensive neuropsychological assessment tool) may be used to diagnose mild to moderately severe Alzheimer's disease. For continuing treatment, patients must demonstrate a two-point increase in MMSE or a four-point increase in ADAS-cog. After the first six months, if an improvement is demonstrated, GPs can subsequently write prescriptions for rivastigmine transdermal patch.

Some groups of patients with an MMSE below 10 are still able to access rivastigmine patches including those with a nonEnglish speaking background, limited education (less than six years), intellectual disabilities or significant sensory impairment despite best correction. Aboriginal or Torres Strait Islanders may also qualify under this criteria. Although PBS subsidies only cover treatment of Alzheimer's disease, there is evidence that patients with some other forms of dementia may respond to rivastigmine.

How to switch from oral formulation

Patients with mild to moderately severe Alzheimer's disease who have been previously treated with rivastigmine capsules or syrup may be switched to the transdermal formulation. An oral dose of less than 6 mg rivastigmine is equivalent to the 9 mg patch (5 cm^2; delivering 4.6 mg/24 hours). Patients taking 6 mg or more of oral rivastigmine can be switched to the 18 mg patch (10 cm^2; delivering 9.5 mg/24 hours). The first patch should be applied the day following the last oral dose.

What needs to be monitored?

Because of the PBS requirements cognitive function must be monitored (using MMSE or ADAS-cog) in patients using the rivastigmine patch during the initial stages. No particular blood tests are required, but one should be vigilant for side effects especially for postural hypotension and bradycardia.

Side effects

Side effects were shown to be similar to placebo with use of both patch sizes, although 2.4% of patients were unable to tolerate the patch due to skin irritation. Common adverse reactions to the rivastigmine transdermal patch include gastrointestinal upset, anorexia, weight loss, anxiety, depression, delirium, urinary urgency, headache, postural hypotension and syncope.

Important precautions and interactions

There is some evidence that interruptions to therapy of two weeks or longer can result in irreversible deterioration. A rare but important side effect of ACHEIs is atrioventricular conduction block. If this occurs the initial treatment would be to discontinue any other medications contributing to the bradycardia including amiodarone, calcium antagonists and antiarrhythmics. If the patient has an atrioventricular conduction block, but has had a very good response to the ACHEIs, a pacemaker may be considered in some cases. The use of cholinomimetics, anticholinergics, neuromuscular blockers (e.g. succinylcholine) and nicotine should be avoided in all patients taking ACHEIs.

Summary

Cholinesterase inhibitors have a PBS listing for mild to moderate dementia, and provide a modest but often clinically significant improvement for people with Alzheimer's dementia. The transdermal formulation of rivastigmine has been shown to minimise gastrointestinal side effects in clinical trials. This transdermal formulation will also allow more patients to benefit from antidementia medication, particularly those reluctant to take oral medications. MT

Further reading

Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 2004; 351: 2509-2518.

Winblad B, Grossberg G, Frölich L, et al. IDEAL: A 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. Neurology 2007; 69(Suppl 1): S14-S22.

Winblad B, Kawata AK, Beusterien KM, et al. Caregiver preference for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease. Int J Geriatr Psychiatry 2007; 22: 485-491.

COMPETING INTERESTS: Associate Professor Caplan has served as a paid speaker or consultant for Pfizer, Janssen and Lundbeck. Dr Kelly: None.